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Ticlopidine-Induced Aplastic Anemia: Development of Chromosomal Abnormalities and Response to Immunosuppressive Therapy

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Severe aplastic anemia is a well-recognized complication of ticlopidine therapy that carries a high mortality. Therapy with colony-stimulating factors or corticosteroids has been largely ineffective in this disorder. We report a case of ticlopidine-induced aplastic anemia that was successfully treated with cyclosporine and high-dose dexamethasone. The patient rapidly responded to immunosuppressive therapy and had a normal hemogram after cessation of immunosuppression. On long-term follow-up, the patient developed a progressive macrocytic anemia. Repeat bone marrow evaluation demonstrated myelodysplasia with erythroid hypoplasia. An associated chromosomal abnormality consisting of a t(3;16) (q21; p13.3) translocation was detected. This is the first report of a chromosomal abnormality associated with ticlopidine induced marrow aplastic anemia. Am. J. Hematol. 63:141–144, 2000. © 2000 Wiley-Liss, Inc.

Key words: ticlopidine; aplastic anemia; immunosuppressive therapy; cyclosporine

INTRODUCTION

Ticlopidine is a thienopyridine antiplatelet agent that inhibits ADP-induced platelet aggregation [1]. It is thought to mediate this effect by the binding of its metabolite(s) to the low-affinity type 2 purinergic ADP receptor, inhibiting platelet activation [1]. Licensed for the secondary prevention of stroke in patients who do not respond to or who are intolerant of aspirin, ticlopidine has also been shown to be effective in cardiovascular [2] and peripheral vascular thrombosis [3]. The drug has been shown to be particularly effective in preventing coronary stent thrombosis [4] and is commonly used for this purpose.

Toxicities frequently reported with ticlopidine therapy include diarrhea, rash, and neutropenia [5]. Other hematologic toxicities associated with ticlopidine treatment include bleeding, thrombocytopenia, thrombotic thrombocytopenic purpura, and aplastic anemia [1]. Aplastic anemia, although rare, can be a fatal complication of ticlopidine therapy. Treatment for this complication is rarely effective. We report a case of ticlopidine-induced aplastic anemia successfully treated with immunosuppressive therapy using cyclosporine and dexamethasone. Long-term follow up of our patient documented an evolution into a myelodysplastic syndrome with an associated chromosomal abnormality.

CASE REPORT

An 80-year-old Caucasian male first presented to our institution on 6 April 1996 with sudden onset of facial drooping and left-sided weakness. He had a history of long-standing hypertension and a hemorrhagic infarct in the right middle cerebral artery. His medications were enalapril (10 mg daily) and aspirin (325 mg daily). Examination revealed left hemiparesis. Magnetic resonance imaging of the brain revealed an acute right middle cerebral artery territory infarct and evidence of old infarction and hemorrhage in the right basal ganglia. Magnetic resonance angiography showed 70% stenosis of the right

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TABLE I. Hematologic Laboratory Values

	04/06/96	05/30/96	06/03/96	06/09/96	08/14/96	06/25/98
Hemoglobin (g/dL)	14.3	10.3	8.8	7.4	15.2	10.1
Hematocrit (%)	43.2	28.4	25.4	20.7	44.7	28.5
Mean corpuscular volume (fL)	94	97	93	91	99.4	99
Red cell distribution width (%)	14.6	12.9	13.1	14	17.2	13.6
White cell count (per mm^3)	6,800	1,200	1,000	6,400	7,500	6,800
Differential (%)						
Neutrophils	59.2	2.2	20.9	79.6	65	65.3
Lymphocytes	28.6	79.1	62.6	15.1	22	23.4
Monocytes	9.7	10.7	6	4.8	11	7.8
Eosinophils	2.2	7.4	10.1	0.4	2	3.1
Basophils	0.3	0.6	0.4	0.1	0	0.4
Platelet count (per mm^3)	169,000	89,000	53,000	43,000	202,000	194,000
Reticulocyte count (% corrected)			0.2	1.7		1.8

internal carotid artery. His hemogram is shown in Table I. Other laboratory studies including electrolytes, renal function, and liver function tests were normal. He was started on ticlopidine 250 mg p.o. b.i.d., and aspirin was discontinued. During his hospital stay, his weakness improved and he was discharged. His blood counts were monitored every 2 weeks.

He was readmitted on 29 May 1996 with a fever of 101°F. He denied localizing symptoms or bleeding from any site. Examination was unremarkable except for mild left hemiparesis and central seventh nerve paresis. Hemogram showed pancytopenia (Table I). Serum chemistries were normal, and hepatitis B surface antigen and hepatitis C antibody studies were negative. Antinuclear antibody titer was 1:80 with a speckled pattern. Ticlopidine had been stopped 4 days prior to this admission when he was found to have neutropenia (WBC: 2200/mm^3) during a periodic blood test. Treatment with G-CSF, 300 μg subcutaneous daily, was started at that time. On admission he was treated with ceftazidime for febrile neutropenia and G-CSF was continued. Bone marrow examination revealed a severely hypocellular marrow with marked decrease in myeloid and erythroid elements with rare megakaryocytes with hypolobated nuclei. Plasma cells and lymphocytes comprised about 30% of total cells. Cytogenetic examination of the bone marrow aspirate showed a normal karyotype. A diagnosis of ticlopidine-induced aplastic anemia was made.

Despite G-CSF therapy, his pancytopenia worsened (Table I) and on 3 June 1996, he was started on oral cyclosporine (5 mg/kg/day), iv dexamethasone at 40 mg/day for 4 days, followed by prednisone 1 mg/kg/day. The patient's neutropenia responded rapidly with resolution of his fever (Table I). He was subsequently discharged in a stable condition. His pancytopenia progressively resolved (Table I), and cyclosporine and steroids were stopped in August 1996.

He continued to do well until June 1998, when after a successful right carotid endarterectomy, he was noticed to have macrocytic anemia. His hemogram is shown in Table I. Serum vitamin B_{12} and folate levels were normal. Bone marrow examination showed a hypocellular bone marrow with megaloblastic-appearing red cell precursors and dysplastic myeloid precursors consistent with myelodysplasia (refractory anemia type). Cytogenetics showed a clonal population characterized by an abnormal translocation, t(3;16) (q21; p13.3) (Fig. 1). Since he was asymptomatic without neutropenia or thrombocytopenia, no specific therapy was given.

DISCUSSION

Hematologic complications have been frequently reported in patients receiving ticlopidine [5]. Neutropenia is the most commonly reported hematologic complication of treatment. Neutropenia with an absolute neutrophil count <1200/mm^3 has been observed in 2.4% of patients, and severe neutropenia with an absolute neutrophil count <450/mm^3 occurred in 0.9% patients [5]. Other reported complications include bleeding, thrombocytopenia, thrombotic thrombocytopenia purpura, and aplastic anemia.

Aplastic anemia is the most dangerous complication of ticlopidine therapy. It is severe, prolonged, and often fatal due to infectious complications. In a recent review of 19 reported cases [6,9–15], the case fatality rate was 42% (8/19). The patients ranged in age from 51 to 85 years, and aplastic anemia occurred from 4 weeks to 3 months after initiation of therapy. The bone marrow aplasia in our patient also occurred within this time period. The patients who died were significantly older than those who survived (mean age 76.3 years vs 67.1 years, $P = 0.021$). No other factor, including treatment with myeloid growth factors (G-CSF or GM-CSF), was found to predict the outcome. The predisposing factors for ticlopidine-induced neutropenia and aplastic anemia are not known.

Ticlopidine-induced neutropenia usually responds to cessation of therapy. Although monitoring of complete blood counts every 2 weeks for at least the first 3 months

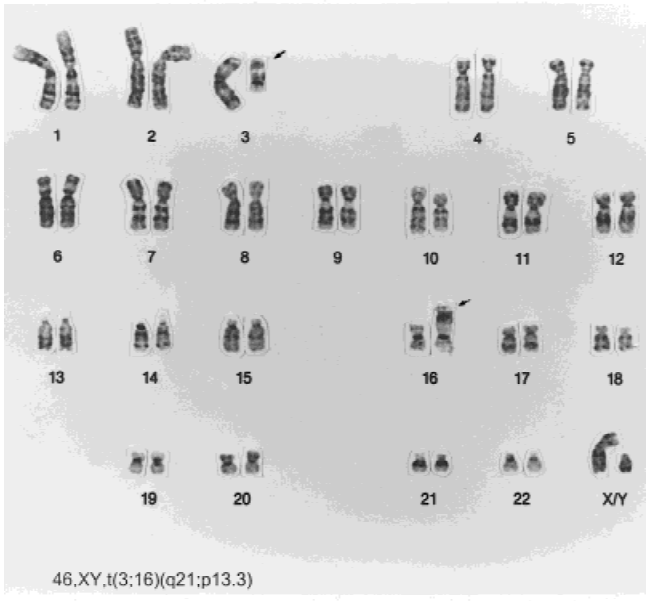

Fig. 1. Cytogenetic study performed on bone marrow of 6/25/98 showing a clonal translocation.

and immediate cessation of the drug, if neutropenia occurs, is recommended [7], this may not prevent aplastic anemia in susceptible individuals, as illustrated by our patient.

The pathogenesis of ticlopidine-induced neutropenia and aplastic anemia is unknown. Both immune and nonimmune mechanisms have been postulated. Ono et al. [8] studied the effects of ticlopidine on CFU-C from T cell depleted marrow of a patient with agranulocytosis and compared it to normal controls. There was a significant dose-dependent reduction in CFU-C of patient's marrow even at very low concentrations of ticlopidine (4–400 ng/mL). The steady-state serum concentration of ticlopidine after an oral dose of 250 mg b.i.d. for 2 weeks ranges from 1.0 to 2.0 μg/mL [9]. There was no effect of the patient's serum or cultured T cells on CFU-C in the presence of ticlopidine. The study above shows that ticlopidine and not its metabolites is responsible for the direct toxic effect on the marrow, resulting in neutropenia. The cause of the exquisite sensitivity of patients' marrow precursors to ticlopidine is not known. The dose dependency favors a direct toxic effect in susceptible individuals with a genetic predisposition determining overall bone marrow sensitivity. In contrast, the idiosyncratic nature of ticlopidine associated aplastic anemia favors either a unique susceptibility in certain individuals or an immune mechanism.

Therapy of ticlopidine-induced aplastic anemia with colony-stimulating factors (G-CSF or GM-CSF) or steroids have shown poor results with a continued high mortality and a slow recovery of marrow function in surviving patients. Of 10 patients reported in the literature who were treated with colony-stimulating factors alone, 6 had a fatal outcome [6,10]. Among the 4 patients treated with high-dose steroids, one died [11] while the other three recovered after ten [12], thirty [13], and fifty-four [14] days, respectively, with the last patient recovering only partially. Two of these patients also received G-CSF [11,14]. While the small number of patients treated precludes drawing any firm conclusions about the effectiveness of these therapies, the apparent improved survival in the steroid-treated patients favors the theoretical use of immunosuppressive therapy.

Considering the success of immunosuppressive therapy in the treatment of idiopathic aplastic anemia [16], and the possible immune mechanism for ticlopidine-induced bone marrow aplasia, we tried therapy with cyclosporine with high-dose dexamethasone. The target blood level of cyclosporine was similar to that utilized in a treatment protocol for idiopathic aplastic anemia [16]. The rapid and sustained response observed in our patient is unusual for ticlopidine-induced aplastic anemia and has not been seen with other reported patients. Although our result needs to be confirmed in more patients, we suggest cyclosporine with high-dose steroids as first-line therapy for ticlopidine-induced aplastic anemia.

The occurrence of myelodysplasia with a clonal chromosomal translocation in our patient 2 years after therapy with ticlopidine may be an independent event. However, it is also consistent with other reports of myelodysplasia and/or paroxysmal noctural hemoglobinuria following recovery from bone marrow aplasia [17,18]. This would suggest that ticlopidine-associated aplastic anemia may result from genomic injury to the multipotential hematopoietic stem cell.

The t(3;16) (q21; p13.3) translocation found in our patient has not previously been described. However, abnormalities of chromosome 3q involving breakpoints 3q21 and 3q26 occur in 2% of myeloid malignancies with karyotypic abnormalities [19]. These are associated with trilineage myelodysplasia with marked abnormalities of the megakaryocyte lineage [19]. The 3q21 breakpoint involves a site 3′ of the ribophorin I gene [20]. 16p13 is the site of the myosin smooth muscle heavy chain gene, which is also a common breakpoint in acute myeloid leukemia.

Clopidogrel is a new antiplatelet agent with structural similarity to ticlopidine and a similar mechanism of action [1]. In a large randomized trial [21], clopidogrel was shown to be superior to aspirin in patients with ischemic stroke, myocardial infarction, and peripheral vascular disease and is indicated for these conditions. Clopidogrel is likely to replace ticlopidine in the future as its side-effect profile is much more favorable, with severe neutropenia occuring only in 0.1% of patients, a rate similar to aspirin [21]. We suggest that clopidogrel be used in situations where ticlopidine is indicated, except for pre-

venting coronary stent thrombosis, as studies have not been completed using clopidogrel for this purpose. The use of ticlopidine for this indication is associated with lower incidence of hematologic toxicity, probably due to the short duration of therapy [1].

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